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Optimal Peak Systolic Velocity Threshold at Duplex US for Determining the Need for Carotid Endarterectomy: A Decision Analytic Approach[1]

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Purpose: To determine the optimal peak systolic velocity (PSV) threshold at duplex ultrasonography (US) required to establish the need for carotid endarterectomy in symptomatic patients on the basis of the long-term cost-effectiveness outcomes of diagnostic testing and subsequent treatment.

Materials and Methods: From January 1997 through January 2000, a prospective medical ethics committee–approved multicenter study was conducted. After giving informed consent, patients with amaurosis fugax, transient ischemic attack, or minor stroke who underwent duplex US and digital subtraction angiography were included in the study. Selective ipsilateral carotid angiograms were obtained in at least three planes. Arteries that were nearly or totally occluded at duplex US were excluded because the PSV cannot be reliably measured in these vessels. Receiver operating characteristic (ROC) curves were constructed for the diagnoses of 70%–99% and 50%–99% stenoses. Optimal likelihood ratios were calculated on the basis of lifetime costs and quality-adjusted life-years derived at cost-effectiveness analysis and the prevalence of disease. The associated optimal sensitivities, specificities, and PSV thresholds were derived from the ROC curves.

Results: In this clinical study, 350 patients were included. The nonoccluded arteries in a total of 236 patients were assessable for ROC analysis. For the diagnosis of 70%–99% stenosis, the optimal likelihood ratio was 0.21, which was associated with a PSV threshold of 220 cm/sec, a sensitivity of 97% (127 of 131 patients; 95% confidence interval [CI]: 94%, 100%), and a specificity of 48% (50 of 105 patients; 95% CI: 38%, 57%). For the diagnosis of 50%–99% stenosis, the optimal likelihood ratio was 0.38, which was associated with a PSV threshold of 180 cm/sec, a sensitivity of 95% (182 of 191 patients; 95% CI: 92%, 98%), and a specificity of 69% (31 of 45 patients; 95% CI: 55%, 82%).

Conclusion: On the basis of the lifetime outcomes of diagnostic testing and subsequent treatment, the optimal PSV thresholds for the diagnosis of 70%–99% and 50%–99% carotid artery stenoses in patients with amaurosis fugax, transient ischemic attack, or minor stroke were 220 cm/sec and 180 cm/sec, respectively.

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The results of two large randomized trials—the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial—have shown carotid artery endarterectomy to yield a considerable benefit in patients with 70%–99% stenosis and a small benefit in patients with 50%–69% stenosis (1–6). In these trials, severe carotid artery stenosis was diagnosed by using cerebral angiography, the reference-standard examination. However, cerebral angiography is associated with a risk of mortality and morbidity and a marked financial cost. The routine use of cerebral angiography in patients with amaurosis fugax, transient ischemic attack, or minor stroke who are potential endarterectomy candidates is therefore undesirable. Consequently, many clinicians now use noninvasive examinations such as duplex ultrasonography (US), magnetic resonance (MR) angiography, and computed tomographic (CT) angiography to select patients for carotid endarterectomy (7). In a cost-effectiveness analysis, we recently found duplex US to be the optimal test strategy for selecting patients suitable for carotid endarterectomy (8).

Moreover, the Society of Radiologists in Ultrasound (SRU) has published recommendations for the interpretation of duplex US results in the diagnosis of internal carotid artery stenosis (7). These recommendations are based on the test characteristics and diagnostic accuracy of duplex US reported in the literature. In most of the diagnostic studies reviewed by the SRU, the optimal threshold of the peak systolic velocity (PSV) was based on the maximization of diagnostic accuracy. With maximization of accuracy as a criterion, one assumes that a false-negative test result has the same importance as a false-positive result. However, because the duplex US result is used to determine whether or not carotid endarterectomy will be performed, the consequences of missing a significant stenosis may be more or less favorable in terms of cost and/or effectiveness outcomes than the consequences of performing endarterectomy for a nonsignificant stenosis. Therefore, it is more clinically relevant to account for the costs and treatment effectiveness associated with false-positive and false-negative test results when selecting an optimal threshold for referring patients for endarterectomy.

Accordingly, the aim of our study was to determine the optimal PSV threshold at duplex US required to establish the need for carotid endarterectomy in symptomatic patients on the basis of the long-term cost-effectiveness outcomes of diagnostic testing and subsequent treatment.

Materials and Methods

Study Population

From January 1997 through January 2000, a prospective diagnostic study was performed at two academic hospitals (University Medical Center Utrecht and Erasmus MC-University Medical Center Rotterdam) and one nonacademic hospital (Medical Spectrum Twente, Enschede, the Netherlands) (9). In this study, 350 patients with a mean age of 67 years (range, 39–88 years) were included and 76% (n = 266) of them were male (9). Two hundred forty-nine of these subjects were patients at University Medical Center Utrecht, 62 were patients at Erasmus MC-University Medical Center Rotterdam, and 39 were patients at Medical Spectrum Twente. After giving informed consent, patients with amaurosis fugax, transient ischemic attack, or minor stroke underwent carotid duplex US and carotid digital subtraction angiography (DSA) within a time frame of 4 weeks. The medical ethics committee at each hospital approved the study.

Duplex US of Carotid Arteries

In the majority of patients (n = 311 [89%]), duplex US was performed with an Ultramark 9 HDI or HDI 3000 (Advanced Technology Laboratories, Bothell, Wash) machine. For the 39 remaining patients, a Diasonics Master Series (GE Medical Systems, Milwaukee, Wis) unit was used. The Doppler angle was aligned to the jet and kept below 60°. The pulsed Doppler gate was positioned in the center of the common carotid artery, approximately 2 cm proximal to the carotid artery bifurcation, and a spectral waveform was obtained. Subsequently, the area with the most severe stenosis was located by using color Doppler US, and a Doppler spectral waveform was obtained at the point of the greatest mean frequency shift. From this spectrum, the PSV of the internal carotid artery was derived. Duplex US examinations were performed by qualified vascular technologists in the vascular laboratory of each hospital. The PSV was measured on a continuous scale, in centimeters per second, in the proximal region of the symptomatic internal carotid artery of each patient. A carotid artery was deemed to be symptomatic when the neurologic symptoms—specifically, amaurosis fugax, transient ischemic attack, or minor stroke—corresponded to the stenotic side. If no detectable blood flow was present, the patient was judged to have an occlusion—that is, 100% stenosis. Slow flow in combination with a visualized severe stenosis was defined as near occlusion. Arteries that were occluded or nearly occluded at US were excluded from re-

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Abbreviations:
CI = confidence interval
DSA = digital subtraction angiography
NASCET = North American Symptomatic Carotid Endarterectomy Trial
NHB = net health benefit
PSV = peak systolic velocity
QALY = quality-adjusted life-year
ROC = receiver operating characteristic
SRU = Society of Radiologists in Ultrasound

Author contributions:
Guarantor of integrity of entire study, M.G.M.H.; study concepts, all authors; study design, M.G.M.H.; literature research, M.H.H.; clinical studies, P.J.N., Y.v.d.G.; data acquisition, P.J.N., E.B.; data analysis/interpretation, M.H.H., M.G.M.H.; statistical analysis, M.H.H., M.G.M.H.; manuscript preparation, M.H.H.; manuscript definition of intellectual content, editing, revision/review, and final version approval, all authors

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ceiver operating characteristic (ROC) analysis, because PSV cannot reliably be measured in these vessels.

DSA Examination

DSA was performed by using an Integris V3000 or Poly-I (Philips Medical Systems, Best, the Netherlands) angiographic unit with an image intensifier matrix of 1024 × 1024. In eight patients, an Angiostar Plus (Siemens Medical Systems, Forchheim, Germany) unit was used. Selective positioning of an intraarterial catheter in the common carotid artery was performed by using the Seldinger technique. From the carotid artery bifurcation, three projections (lateral, posteroanterior, and oblique) were acquired. The additional projections obtained at occasionally performed rotational DSA examinations were not used in this study. For each projection, 6 mL of iopromide (Ultravist 300; Schering, Berlin, Germany) was injected at a flow rate of 3 mL/sec or 9 mL of iomeprol (Iomeron 350; Altana Pharma, Hoofddorp, the Netherlands) was injected at a flow rate of 6 mL/sec.

The DSA results were read by two radiologists, each of whom had more than 5 years of experience. The observers were blinded to the patients' clinical information and duplex US results. They read the film hard copies of the DSA images. The stenosis percentage was measured according to NASCET criteria (1). Degree of stenosis was defined as the remaining lumen at the site of the stenosis divided by the normal lumen distal to the stenosis. Stenosis of 99% was defined as near occlusion. The maximal degree of stenosis seen on the three projections was used in the analyses. DSA was considered the standard of reference. Interobserver agreement regarding data obtained in a representative sample of 170 patients was determined by calculating κ values.

Markov Model

The lifetime costs and quality-adjusted life-years (QALYs) rendered after obtaining true-positive, false-positive, true-negative, and false-negative duplex US results were derived by using a previously described Markov model (8). These values included the costs and utilities associated with the subsequent treatment, treatment complications, and progression of disease that ensued after these results were obtained. Several health states were modeled for the severity of neurologic disease (ie, transient ischemic attack, minor stroke, or major stroke as a presenting condition or a complication) in patients who initially had less than 50% stenosis, 50%–69% stenosis, or 70%–99% stenosis. Medical therapy, including aspirin treatment, was assumed to be the optimal treatment for patients with less than 50% stenosis. For patients with greater than 50% stenosis, two criteria for carotid endarterectomy referral were considered: 70%–99% stenosis and 50%–99% stenosis. We assumed that the associated costs and life expectancy after a carotid endarterectomy depended on the presenting symptoms (ie, transient ischemic attack or minor stroke) rather than on the patient's underlying stenosis category before surgery. Disease progression and death were modeled by simulating transitions to more severe health states during follow-up. The Markov model was constructed by using DATA Pro 11.0 software (TreeAge, Williamstown, Mass). The lifetime costs and effects were integrated into one measure, the net health benefit (NHB), which is derived by using the following equation:

$$NHB = E_{QALY} - (C/T_{WTP}), \qquad (1)$$

where E_{QALY} represents the lifetime effects in QALYs, C represents the lifetime costs, and T_{WTP} is the amount that society is willing to pay (ie, willing-to-pay threshold) to save one QALY (10). With this formula, we assumed two threshold amounts that society would be willing to pay to save one QALY: \$25 000 and \$50 000 per QALY.

Recommended PSV Thresholds

The recommended PSV thresholds of 230 cm/sec for the diagnosis of 70%–99% stenosis and 125 cm/sec for the diagnosis of 50%–99% stenosis were applied to our study data (7). For both PSV thresholds, we calculated the associated sensitivity and specificity.

Optimal PSV Threshold at Statistical Analysis

We calculated the sensitivities and specificities associated with different PSV thresholds by using DSA as the reference-standard examination. We used two definitions of carotid artery disease, which corresponded to the two indications for referring patients for carotid endarterectomy: angiographically determined 70%–99% stenosis and 50%–99% stenosis. The cost-effectiveness outcomes of the Markov model for the 50%–69% stenosis category were combined with the results of either the 0%–49% category or the 70%–99% category (weighted for prevalence), depending on the indication for carotid endarterectomy. With use of ROC analysis, all combinations of sensitivity and specificity were plotted on a graph on which the y-axis represented sensitivity and the x-axis represented 1 − specificity (11). Smooth ROC curves were created by using summary ROC analysis methods (12–14). For each combination of sensitivity and specificity on the smooth curves, the result-specific likelihood ratio (LR_{Ri})—that is, the probability *(P)* of a specific test result *(Ri)* (eg, a PSV of 220 cm/sec) in the group with the disease (DG) divided by the probability of that specific test result (eg, 220 cm/sec) in the group without the disease (NDG)—was calculated and was equal to the tangent, or the slope of the curve (15,16):

$$LR_{Ri} = \frac{P(Ri|DG)}{P(Ri|NDG)}. \qquad (2)$$

With the lifetime consequences of diagnostic testing and subsequent treatment taken into account, the optimal likelihood ratio (LR_{opt}) depends on the prevalence of disease *(p)* and the ratio of the net loss due to false-positive test results compared with true-negative results ($NHB_{TN} - NHB_{FP}$) to the net loss due to false-negative results compared with true-positive results ($NHB_{TP} - NHB_{FN}$) (15–17):

$$LR_{opt} > \frac{1-p}{p} \cdot \frac{NHB_{TN} - NHB_{FP}}{NHB_{TP} - NHB_{FN}}. \qquad (3)$$

The optimal combination of sensitivity and specificity (ie, the optimal operating point) was derived from the smooth ROC curve at the operating point where the result-specific likelihood ratio (Eq [2]) equaled the optimal likelihood ratio based on the Markov model (Eq [3]). Subsequently, we selected the PSV value that was observed to be closest to the operating point on the smooth curve and defined it as the optimal PSV threshold.

Sensitivity analysis of the prevalence of significant stenosis was performed to evaluate the effect of this prevalence on the optimal likelihood ratio, sensitivity, specificity, and PSV threshold. We used the SPSS 11.0 statistical software package (SPSS, Chicago, Ill) to perform summary ROC curve analysis and Excel 2000 (Microsoft, Redmond, Wash) to construct the ROC curves.

Results

DSA and Duplex US Results

The symptomatic carotid artery could be imaged and evaluated in 323 patients with DSA and in 330 patients with duplex US. The results of both examinations were available for 313 patients. Values were missing owing to the following reasons: Sometimes it was not feasible to perform both examinations before surgery, some patients withdrew from the study after having undergone one examination, and the examination was not always correctly performed according to our study protocol. Also, occasionally, the PSV was not measured when duplex US was performed. Finally, in seven patients, it was impossible to measure the degree of stenosis because of poor image quality and the poor reliability of the DSA findings. Interobserver agreement calculated on the basis of the DSA results for 170 patients was good ($\kappa = 0.79$; 95% confidence interval [CI]: 0.74, 0.84).

In Table 1, the categorized DSA and duplex US results are cross tabulated. At DSA, 0%–49% stenosis was detected in 45 (14%) of 313 patients, 50%–69% stenosis was detected in 61 (20%), 70%–98% stenosis was detected in 128 (41%), near occlusion (ie, 99% stenosis) was detected in 16 (5%), and occlusion was detected in 63 (20%). Duplex US depicted occlusions in 61 patients. The sensitivity and specificity of the duplex US–based diagnosis of occlusion were 94% (59 of 63 patients; 95% CI: 88%, 100%) and 99% (248 of 250 patients; 95% CI: 98%, 100%), respectively. There was slow flow in combination with visualized severe stenosis at duplex US, indicating near occlusion, in 16 patients. In a total of 236 patients, arteries that were neither occluded nor nearly occluded at duplex US were assessable at ROC analysis.

The data in Figure 1, in which absolute PSV measurements are plotted against angiographic degrees of stenosis, show that the relationship between PSV and stenosis degree is nonlinear. In Figure 1a and 1b, the indications for endarterectomy are set at minimal angiographic stenosis degrees of 70% and 50% (horizontal lines), respectively. Shifting the PSV threshold (vertical lines) to the left would result in an inversely related increase in the number of true-positive test results and a decrease in the number of true-negative test results. Thus, a decreased PSV threshold is associated with higher sensitivity and lower specificity. Conversely, shifting the PSV threshold upward would result in lower sensitivity and higher specificity.

Markov Model

Long-term outcomes of the cost-effectiveness analysis (Table 2) indicate that referring patients for carotid endarterectomy instead of medical therapy resulted in a loss in QALYs and an increase in costs for patients with 0%–49% stenosis. Performing endarterectomy facilitated a small gain in QALYs and a slight cost savings in patients with 50%–69% stenosis and a relatively large gain in QALYs and a large cost savings in patients with 70%–99% stenosis (Table 2).

Recommended PSV Thresholds

The SRU has recommended using a PSV of 230 cm/sec for the diagnosis of 70%–99% stenosis and a PSV of 125 cm/sec for the diagnosis of 50%–99% stenosis (7). Applying the recommended threshold of 230 cm/sec to diagnose 70%–99% stenosis in our population would result in a sensitivity of 95% (125 of 131 patients; 95% CI: 92%, 99%) and a specificity of 51% (54 of 105 patients; 95% CI: 42%, 61%). If we applied a threshold of 125 cm/sec to detect 50%–

Table 1

Categorized Internal Carotid Artery Measurements at Duplex US versus DSA

Duplex US Stenosis Category	DSA Stenosis Category: 0%–49%	50%–69%	70%–98%	99%	Occlusion	Total
PSV (cm/sec)						
0–124	16	1	0	0	0	17
125–230	20	17	5	1	0	43
>230	8	42	117	8	1	176
Near occlusion	1	1	5	6	3	16
Occlusion	0	0	1	1	59	61
Total	45	61	128	16	63	313

Note.—Data are numbers of patients.

Figure 1

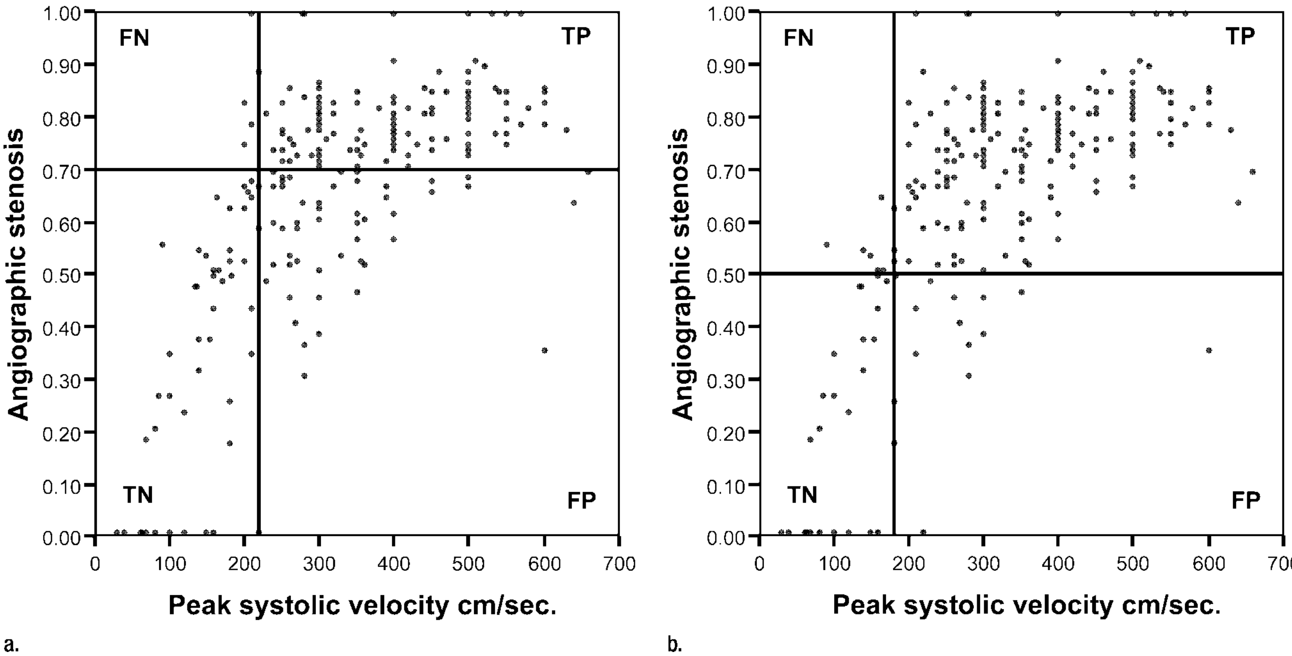


Figure 1: Scatterplots of absolute PSV measurements and angiographic stenosis measurements. PSV thresholds for referring patients with **(a)** 70%–99% stenosis (220 cm/sec) and **(b)** 50%–99% stenosis (180 cm/sec) for carotid endarterectomy are shown. Increasing the PSV threshold reduces the number of false-positive *(FP)* cases (higher specificity) at the expense of a higher number of false-negative *(FN)* cases (lower sensitivity). *TN* = true-negative cases, *TP* = true-positive cases.

99% stenosis in our study population, the sensitivity would be 99% (190 of 191 patients; 95% CI: 98%, 100%) and the specificity would be 36% (16 of 45 patients; 95% CI: 22%, 50%).

Optimal PSV Thresholds

For a referral for endarterectomy based on an indication of 70%–99% stenosis, the optimal result-specific likelihood ratio based on the Markov model (calculated by using Eq [3]) was 0.21. Figure 2a shows the observed ROC curve and the smooth ROC curve. Each dot on the observed curve represents the sensitivity and 1 − specificity of a specific PSV threshold for the angiographic diagnosis of 70%–99% stenosis—that is, for the eligibility for endarterectomy. The optimal likelihood ratio, or the slope of the ROC curve, is illustrated in this figure. The associated optimal sensitivity and specificity were 97% (127 of 131 patients; 95% CI: 94%, 100%) and 48% (50 of 105 patients; 95% CI: 38%, 57%), respectively. The optimal PSV threshold that corresponded to this sensitivity and specificity was 220 cm/sec (Fig 2a). The optimal PSV threshold is illustrated in Figure 1a also. The bottom right quadrant of this figure shows the large number of false-positive test results obtained by using the optimal PSV threshold compared with the top left quadrant, which contains a small number of false-negative test results obtained by using the optimal PSV threshold.

When 50%–99% stenosis was used to indicate the need for endarterectomy, the optimal result-specific likelihood ratio was 0.38. The associated optimal sensitivity and specificity were 95% (182 of 191 patients; 95% CI: 92%, 98%) and 69% (31 of 45 patients; 95% CI: 55%, 82%), respectively (Fig 2b). The optimal PSV threshold that corresponded to this sensitivity and specificity was 180 cm/sec (Figs 1b, 2b).

Changing the willingness-to-pay threshold from \$25 000 to \$50 000 per QALY hardly affected the optimal likelihood ratio and thus had no effect on the optimal PSV threshold. When a higher willingness-to-pay threshold is accepted, the NHB (Eq [1]) increases. The ratio of the difference in NHBs associated with specific test results, however, changed only minimally when a higher willingness-to-pay threshold was used (Eq [3]).

The results of the sensitivity analysis of the prevalence of disease are shown in Table 3. The data in this table demonstrate that when the prevalence of significant stenosis increases, the optimal likelihood ratio decreases and corresponds to higher sensitivity, lower specificity, and a decreased optimal PSV threshold. The data in Table 3 also show that the prevalence of significant disease (50%–99% stenosis) has to be very high (approximately 90%) before the threshold of 125 cm/sec recommended by the SRU becomes optimal.

Discussion

We found that the optimal PSV threshold for selecting symptomatic patients for carotid endarterectomy was 220 cm/sec when the indication for endarterectomy was 70%–99% stenosis and 180 cm/sec when the indication was

50%–99% stenosis. The 220 cm/sec threshold is similar to the threshold recommended by the SRU (230 cm/sec for 70%–99% stenosis), but 180 cm/sec is higher than the recommended threshold (125 cm/sec for 50%–99% stenosis) (7).

The SRU based its recommendations on literature review findings. The studies included in that review were focused on optimizing accuracy, and the participating investigators did not take into account the variable effects of false-negative test results as opposed to the effects of false-positive test results. The results of our study show that referring a patient with nonsignificant stenosis (<50%) for endarterectomy is more harmful than missing a diagnosis of 50%–69% stenosis, and this finding explains the fairly high PSV threshold for discriminating 50%–99% stenosis from 0%–49% stenosis.

The natural history of the disease to be identified and the effectiveness of treatment have a major role in determining the importance of sensitivity and specificity. In cases of high-grade (>70%) carotid artery stenosis especially, undiagnosed disease is associated with high monetary and life expectancy costs (8). For the identification of patients with high-grade stenosis, duplex US criteria should be highly sensitive, yielding a minimal number of false-negative results, because these patients will have high degrees of morbidity and mortality if they are left untreated. The overall losses associated with missing a diagnosis in patients with 50%–99% stenosis are smaller, because the benefits associated with 50%–69% stenosis are smaller than those associated with 70%–99% stenosis. Balancing the losses and benefits led to a somewhat lower optimal sensitivity and a higher optimal specificity for the identification of 50%–99% stenosis compared with the identification of 70%–99% stenosis.

The prevalence of significant stenosis in the population being evaluated also has a critical role in defining the optimal test criterion. In our study population, the prevalence of 70%–99% stenosis was 46% and the prevalence of 50%–99% stenoses was 66%. Sensitivity analysis revealed that if the prevalence of significant stenosis were lower, the derived slope would be steeper (Eq [3]) and the optimal cutoff point on the ROC curve would shift to the left, implying lower sensitivity, higher specificity, and thus a higher PSV threshold.

Increasing the societal willingness-to-pay threshold from $25 000 to $50 000 per QALY did not influence the choice of the optimal PSV threshold in our study. However, this is not always the case: The optimal likelihood ratio can either increase or decrease—depending on the proportions of true and false results in a particular test situation—and thus lead to a higher or lower threshold when the willingness-to-pay threshold is increased.

Various methods of determining the optimal diagnostic cutoff point on the ROC curve have been reported in the literature. Some investigators have used the point on the curve that is closest to the upper left corner in the ROC space as the optimal cutoff point (18); others have used the cutoff point associated with a likelihood ratio of 1 (19). Other methods include selecting the Q point—that point where sensitivity equals specificity (20); maximizing accuracy, or the sum of the sensitivity and specificity values (21,22); and accepting a preset level of sensitivity (or specificity) and deter-

Table 2

Lifetime Costs, QALYs, and NHBs for Base Cases with Positive and Negative Duplex US Results for Several Stenosis Categories

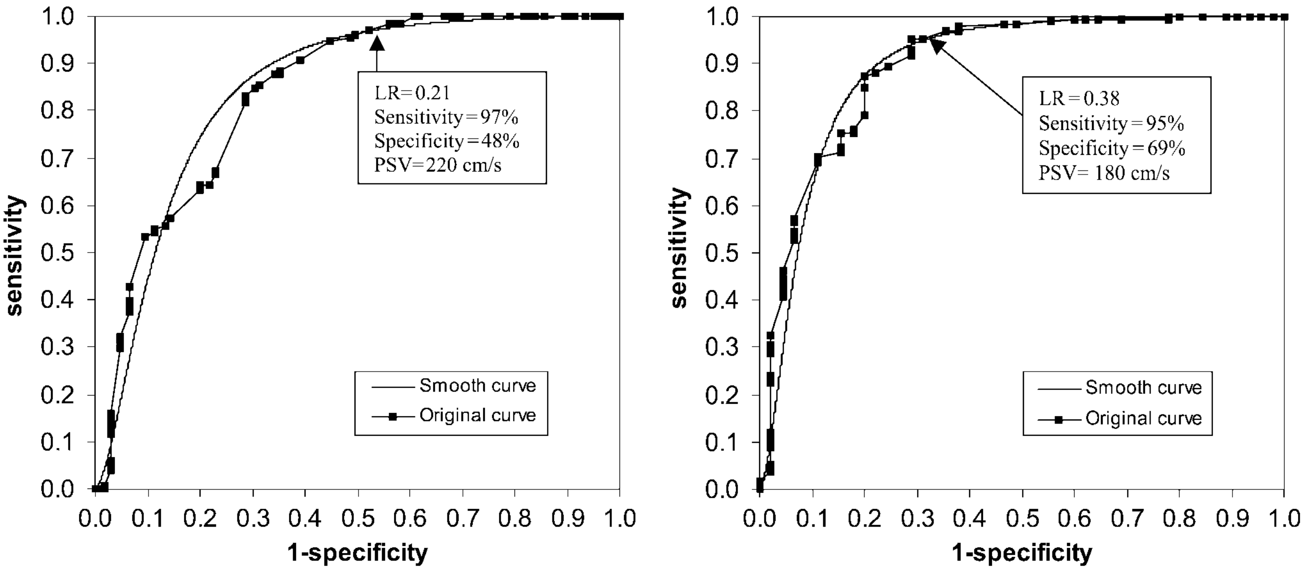
	Stenosis Category		
Stenosis Prevalence and Treatment Scenario*	0%–49%	50%–69%	70%–99%
Prevalence	0.14	0.19	0.46
Negative US result, treatment with medical therapy			
Cost ($)	30 599	36 427	46 444
No. of QALYs	11.36	11.09	10.71
NHB with $25 000 WTP per QALY	10.14	9.63	8.85
NHB with $50 000 WTP per QALY	10.75	10.36	9.78
Positive US result, treatment with carotid endarterectomy†			
Cost ($)	35 638	35 638	35 638
No. of QALYs	11.12	11.12	11.12
NHB with $25 000 WTP per QALY	9.70	9.70	9.70
NHB with $50 000 WTP per QALY	10.41	10.41	10.41
Endarterectomy versus medical therapy			
Change in cost ($)	5139	−789	−10 806
Change in no. of QALYs	−0.24	0.03	0.41
Change in NHB with $25 000 WTP per QALY	−0.44	0.06	0.85
Change in NHB with $50 000 WTP per QALY	−0.34	0.05	0.63

Source.—Reference 8: modified data (from table 3) on treatment and follow-up of patients with TIA or stroke.

* WTP = willingness-to-pay threshold.

† Risks and prognosis following carotid endarterectomy were assumed to be independent of the underlying stenosis category.

Figure 2



a. b.

Figure 2: Observed (ie, original) and smooth ROC curves for indications of **(a)** 70%–99% and **(b)** 50%–99% stenoses. The optimal likelihood ratio *(LR)*—that is, the slope of the ROC curve—derived at cost-effectiveness analysis is indicated with the associated sensitivity, specificity, and optimal PSV threshold. These data show that the optimal operating point on the ROC curve based on cost-effectiveness analysis results is different from the point on the curve that is closest to the upper left corner in ROC space, which is based on maximal accuracy.

mining the corresponding specificity (or sensitivity) (23). All of these methods help to minimize the number of false-positive and false-negative test results. However, none of these methods involves taking into account the prevalence of disease or the consequences—in terms of costs and quality of life—of correctly or incorrectly classifying a test result as positive or negative.

The decision analytic approach of determining the optimal diagnostic threshold that we used was described many years ago (15). Published practical applications of this method, however, are scarce. In publications on carotid artery disease, we found only two studies in which the investigators based their optimal test criteria on patient outcomes rather than test accuracy (24,25). Wilterdink and co-workers (24) based their criteria on the 2-year mortality and morbidity rates associated with severe stenosis treated medically versus surgically, as reported in the NASCET. They observed a slope, or optimal likelihood ratio, of 0.09, which is more lenient than the slope that we observed and implies higher sensitivity and lower specificity. They used duplex US to select patients for angiography, whereas we used duplex US to select patients for endarterectomy.

The harm of performing unnecessary angiography in false-positive cases in the Wilterdink et al study (24) was much smaller than the harm of performing unnecessary endarterectomy in the current study. In both the Wilterdink et al study and the current study, however, the harm of a false-negative test result was the same: missing the opportunity to reduce the probability of a carotid event by means of endarterectomy. These factors explain the lower slope. Furthermore, we used updated results from the NASCET study, which show a small but significant benefit for patients with 50%–69% stenosis; we integrated both costs and effects on life expectancy; and we modeled lifetime outcomes.

Kuntz et al (25) chose the PSV cutoff point that minimized the probability of stroke at 2 years for symptomatic patients. They observed an optimal PSV threshold of 229 cm/sec at one laboratory and 340 cm/sec at another laboratory. They did not report the optimal likelihood ratio, or the slope of the ROC curve. We did not evaluate the potential differences between hospitals. Hospitals that do have data on angiography and PSV measurements, however, could construct their own ROC curve and determine their own optimal threshold by using the optimal slope derived from our decision analysis.

Our study population consisted of patients with transient ischemic attack, minor stroke, or amaurosis fugax. The optimal PSV threshold may vary among patients with different symptoms of carotid disease. We were unable to calculate optimal PSV thresholds for each subgroup of patients because the subgroups were too small for us to derive accurate ROC curves with enough cutoff values that were evenly spread along the curve. Moreover, optimal PSV thresholds may be different for asymptomatic patients, because the associated costs and consequences of testing and treatment for these patients differ from those for symptomatic patients.

For the estimation of ROC curves, the test variable needs to be a measure that continuously increases or decreases with the severity of disease. The PSV, however, increases with the severity of stenosis but decreases with near occlusion and is absent with total occlusion; therefore, we had to exclude these conditions. This was justified in the cases of total occlusion, because carotid endarterectomy is not indicated for totally occluded arteries. Duplex US was most accurate for the diagnosis of the total occlusions but not very accurate for the diagnosis of the near occlusions. Overall, excluding the near and total occlusions did not result in an overestimation of the diagnostic accuracy of duplex US.

Currently, new noninvasive tests that yield excellent images of the carotid arteries, such as CT angiography and MR angiography, are available (26). With the availability of these examinations, preoperative carotid angiography is hardly needed anymore. However, these new examinations are not yet accepted as reference-standard tests; therefore, we used carotid angiography as the reference-standard test in our ROC analyses.

Furthermore, we took into account no velocity parameters except the PSV. In several studies, it has been shown that the PSV in the internal carotid artery is the best single velocity parameter for quantifying stenosis (27,28). In clinical practice, multiple clinical parameters could be combined to account for differences in patients and to decide which patients should undergo carotid endarterectomy.

In our analyses, we used a decision analytic model to calculate the harms and benefits of diagnostic testing and subsequent treatment. This model is a simplification of reality. The input variables came from multiple sources, assumptions had to be made, and uncertainty surrounded the input variables. Thus, when new therapies become available, the model may need to be changed. For example, our calculations are based on the use of aspirin as the optimal medical therapy for symptomatic patients with less than 50% stenosis, in accordance with the NASCET and European Carotid Surgery Trial protocols. However, these patients are increasingly being treated with statins and clopidogrel also. Therefore, the diagnostic thresholds need to be updated when data on the long-term effects of statins and clopidogrel in these patients become available.

In conclusion, on the basis of the lifetime consequences of diagnostic testing and subsequent treatment, the optimal PSV threshold was 220 cm/sec for the diagnosis of 70%–99% carotid artery stenosis and 180 cm/sec for the diagnosis of 50%–99% stenosis in patients with amaurosis fugax, transient ischemic attack, or minor stroke when duplex US was used to refer patients for carotid endarterectomy.

Table 3

Influence of Prevalence of Significant Stenosis on Optimal Likelihood Ratio, Sensitivity, Specificity, and Optimal PSV Threshold

Prevalence of Stenosis*	LR_{opt}†	Sensitivity (%)	Specificity (%)	Optimal PSV Threshold (cm/sec)
	Influence of Significant Stenosis Prevalence for Diagnosis of 70%–99% Stenosis			
0.10, 0.45, 0.45	2.000	73	81	300
0.20, 0.40, 0.40	0.890	87	71	275
0.30, 0.35, 0.35	0.520	92	63	250
0.40, 0.30, 0.30	0.330	95	57	245
0.50, 0.25, 0.25	0.220	96	50	225
0.60, 0.20, 0.20	0.150	98	43	200
0.70, 0.15, 0.15	0.095	99	35	175
0.80, 0.10, 0.10	0.056	99	25	150
0.90, 0.05, 0.05	0.025	100	13	100
	Influence of Significant Stenosis Prevalence for Diagnosis of 50%–99% Stenosis			
0.10, 0.45, 0.45	1.750	82	84	250
0.20, 0.40, 0.40	0.900	90	78	220
0.30, 0.35, 0.35	0.560	93	73	200
0.40, 0.30, 0.30	0.370	95	69	180
0.50, 0.25, 0.25	0.250	96	64	175
0.60, 0.20, 0.20	0.170	97	59	160
0.70, 0.15, 0.15	0.110	98	53	155
0.80, 0.10, 0.10	0.064	99	44	145
0.90, 0.05, 0.05	0.029	100	31	110

* For each series of three prevalence values, the first value is the prevalence of 70%–99% stenosis; the second value, the prevalence of 50%–69% stenosis; and the third value, the prevalence of 0%–49% stenosis.

† LR_{opt} = optimal likelihood ratio.

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